The Examiner's Point 1, states that the "n" is in the wrong place. Applicants apologize for this confusion. The Examiner will note that the methyl in formula II, which the "n" modifies is now written $_n(H_3C)$-, whereas in the original claim, it was written $(CH_3)_n$-. Applicants respectfully submit that the two are equivalent and that, in any event, the present rendering is more accurate because it indicates that the leading bond comes from the carbon, not the hydrogen.

Claim 6 has been amended to remedy Point 2.

Point 3 is a new ground of rejection that the Examiner first raised in an Advisory Action, paper number 31, mailed June 7, 1999. Point 3 questions recitations that were originally present in a dependant claim, but were moved to the independent claims. Because Applicants' mere movement of these claim terms could not now raise new issues relating to their clarity, as alleged by the office, this represents a new rejection. Applicant's, therefore, request the PTO to remove the final rejection and issue a new office action. *See* MPEP § 706.07(a) (final rejection proper only where applicant's amendment necessitated new rejection).

Briefly turning to the merits of this rejection, however, Applicants note that one skilled in the art would readily understand the structure of the recited carbohydrate-bearing molecules. The Examiner admits that acids can form esters (for example, by reaction with alcohols[1]). (Paper 35, p. 2.) As the Examiner will appreciate, all of the carbohydrate moieties at issue have at least one hydroxyl group (*i.e.*, they are alcohols). There are numerous basic chemical protocols, with which the artisan would have been familiar at the time of the present invention, for converting alcohols to acids.[2] Once converted to their corresponding acids, the carbohydrate moieties can undergo the same chemical reactions as the amino acids that were not found objectionable. The artisan will understand, accordingly, the structure of the contemplated molecules and how to make them. Finally, the claims require an "ester linkage" (see claim 1, for example), so the ethers postulated by the Examiner are not recited.

---

[1] See any basic organic chemistry text. One such example is Solomons ORGANIC CHEMISTRY, 3d ed., pp. 794-97 (John Wiley & Sons 1984).

[2] See references cited in the attachment, all of which pre-date the present application.

In their last response, Applicants submitted a declaration made by Dr. Carolyn Paradise that attested to the fact that a clinician could use the claimed compounds and compositions without undue experimentation. The Examiner affords it no weight because it is allegedly based on "conclusions without supporting facts." In drawing this conclusion, the Examiner ignores most of the facts.

The Examiner focuses his attack on the Margolin paper which, he asserts, proves a point contrary to that asserted by Dr. Paradise. This is not so. It is acknowledged that the Margolin paper showed no statistical *correlation* with the doses of lysofylline employed, but they concluded: "It is likely that the lack of toxicity modulation by LSF in our study was due to subtherapeutic plasma levels ...." Contrary to the assertion of the Examiner, this does not prove that LSF is not good for anything. Rather, it shows that LSF is undergoing clinical investigation for at least one indication and that the dose adjusting is required.

The remainder of the evidence presented by Dr. Paradise was ignored. As explained in part by Dr. Paradise, Appendices C, D and E relate to alleviating side effects associated with bone marrow transplantation that interfere with engraftment -- a utility disclosed in the present application and the original lisofylline patent (US Pat No 5,652,243), the disclosure of which is incorporated by reference in the instant specification (p. 1, last ¶). Appendices C and D demonstrate, in a statistically significant manner, that bone marrow transplant recipients develop infections at a lower rate than placebo controls. Appendix E demonstrates statistically significant reduction of graft-versus host disease in a population of bone marrow recipients.

The Examiner claims insufficient basis on which to evaluate these data, but it is unclear what is meant by this. These data indicate dose, levels of statistical significance and patient population size, which are sufficient for skilled clinicians. Moreover, Applicants note that it is the burden of the PTO to substantiate non-enablement, which it has not carried. Applicants merely refer to the present data to counter the PTO's unsubstantiated contention that lisofylline is not "useful for anything."[3] Applicants respectfully submit, therefore, that, contrary

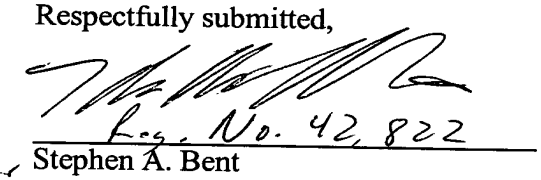
[3] Office Action of 18 October 1996, p. 2, item 3.

to the PTO position, lisofylline is in fact good for something, and the present application is enabling.

CONCLUSIONS

In view of the foregoing, Applicants submit that the present claims are in condition for appeal of the noted rejection as the sole issue. Should the Examiner have any questions regarding the present application or believe that further discussion will further clarify the issues, the Examiner is invited to contact the undersigned at the number listed below.

Respectfully submitted,



for Reg. No. 42,822
Stephen A. Bent
Reg. No. 29.768

October 1, 1999
Date

FOLEY & LARDNER
Suite 500
3000 K Street, N.W.
Washington, DC 20007-5109
(202) 672-5300